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**WO 02/048165 A3**

(54) Title: ANTIVIRAL AGENTS FOR TREATMENT OF FLAVIVIRIDAE INFECTIONS

(57) Abstract: The disclosed invention is a composition for and a method of treating *Flaviviridae* (Hepacivirus, Flavivirus, Pestivirus) infections, including BVDV and HCV, and abnormal cellular proliferation in a host, including animals, and especially humans, using a small molecule or its pharmaceutically acceptable salt or prodrug.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/49231

## A. CLASSIFICATION OF SUBJECT MATTER

|       |            |            |            |           |           |
|-------|------------|------------|------------|-----------|-----------|
| IPC 7 | C07H19/00  | C07H19/207 | C07D307/88 | C07F9/655 | A61K31/70 |
|       | A61K31/343 | A61K31/665 | A61P35/00  |           |           |

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H C07D C07F A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.  |
|------------|---|--|
| X          | <p>WO 94 29331 A (SLOAN KETTERING INST CANCER<br/>;UNIV ROCHESTER (US))<br/>22 December 1994 (1994-12-22)</p> <p>claims 1-3,8,11,22</p> <p>---</p> <p>-/-</p> | <p>1,2,8,9,<br/>15,16,<br/>36,37,<br/>43,44,<br/>50,51,<br/>60-63,68</p> |

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

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24 April 2002

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/49231

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.  |
|----------|---|--|
| X        | WO 98 15563 A (CODON PHARMACEUTICALS INC)<br>16 April 1998 (1998-04-16)<br><br>page 98, line 19; page 99, lines 1,19;<br>page 100, lines 26,29,32; page 101, line<br>3; page 105, line 17; page 106, lines<br>1,17; page 107, lines 10-21; page 23,<br>lines 19-29; page 3, lines 5-19<br>---   | 1,2,8,9,<br>15,16,<br>36,37,<br>43,44,<br>50,51,<br>60-63,68 |
| X        | US 5 658 890 A (PANKIEWICZ KRYSZTOF W ET<br>AL) 19 August 1997 (1997-08-19).<br><br>examples 1,2,7,8; column 2, lines 29-64<br>---  | 1,2,8,9,<br>15,16,<br>36,37,<br>43,44,<br>50,51,<br>60-63,68 |
| X        | LESIAK K ET AL: "SYNTHESIS OF<br>NONHYDROLYZABLE ANALOGUES OF<br>THIAZOLE-4-CABOXAMIDE AND BENZAMIDE ADENINE<br>DI NUCLEOTIDE CONTAINING FLUORINE ATOM AT<br>THE C2' OF ADENINE NUCLEOSIDE: INDUCTION<br>OF K562 DIFFERENTIATION AND INOSINE<br>MONOPHOSPHATE DEHYDROGENASE INHIBITORY<br>ACTIVITY"<br>JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN<br>CHEMICAL SOCIETY. WASHINGTON, US,<br>vol. 40, 1997, pages 2533-2538,<br>XP002920574<br>ISSN: 0022-2623<br>page 2534, compounds 10-12; page 2533,<br>columns 1 and 2<br>--- | 1,2,8,9,<br>15,16,<br>36,37,<br>43,44,<br>50,51,<br>60-63,68 |
| X        | WO 98 34942 A (INSPIRE PHARMACEUTICALS INC<br>;RIDEOUT JANET L (US); PENDERGAST WILL)<br>13 August 1998 (1998-08-13)<br>page 4, Table 1, Ac2C-NAD, Ac2C-PAD,<br>Ap2BAD; page 7, lines 5-14<br>---   | 1,8,15   |
| X        | RILEY T A: "SYNTHESIS OF<br>2-(BETA-D.RIBOFURANOSYL) PYRIMIDINES, A<br>NEW CLASS OF C-NUCLEOSIDES"<br>JOURNAL OF HETEROCYCLIC CHEMISTRY,<br>HETERO CORPORATION. PROVO, US,<br>vol. 24, 1 July 1987 (1987-07-01), pages<br>955-964, XP000575823<br>ISSN: 0022-152X<br>page 958, compound 20<br>---   | 1  |
|          |   | -/-  |

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/49231

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages                   | Relevant to claim No.                          |
|----------|--|--|
| A        | US 4 748 173 A (NELSON PETER H. ET AL)<br>31 May 1988 (1988-05-31)<br><br>abstract; claim 1<br>----- | 1,8,15,<br>22,29,<br>36,43,<br>51-55,<br>60-63 |

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 01/49231

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
**Although claims 22-53,56-68 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**1,2,8,9,15,16,22,23,29,30,36,37,43,44,50-55,60-63,68 partially**

#### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,2,8,9,15,16,22,23,29,30,36,37,43,44,50-55,60-63,  
68 partially

Dinucleoside diphosphate derivatives of formula I, claim 1, wherein R is a nucleoside analogue with a 6-membered heterocycle as defined in formulae II and III; pharmaceutical compositions containing them; uses thereof.

2. Claims: 1,2,8,9,15,16,22,23,29,30,36,37,43,44,50-55,60-63,  
68 partially

Nucleoside diphosphate derivatives of formula I, claim 1, wherein R is a mycophenol derivative with a sidechain of at least 3 C-atoms as defined in formula IV; pharmaceutical compositions containing them; uses thereof.

3. Claims: 3,10,17,24,31,38,45,56-59,  
64-67 completely; claims 1,2,8,9,15,16,22,23,29,30,  
36,37,43,44,50-55,60-63,68 partially

Nucleoside diphosphate derivatives of formula I, claim 1, wherein R is a mycophenol derivative with a C2-sidechain as defined in formula V; pharmaceutical compositions containing them; uses thereof.

4. Claims: 2,9,16,23,30,37,44,50-55,60-63,68 partially

Thiazofuran derivatives as defined in claim 2; pharmaceutical compositions containing them; uses thereof.

5. Claims: 4,11,18,25,32,39,46,50-55,60-63,68 partially

Derivatives of mycophenolic alcohols, aldehydes and acids with a C2-sidechain as defined in claim 4; pharmaceutical compositions containing them; uses thereof.

6. Claims: 4,11,18,25,32,39,46,50-55,60-63,68 partially

Derivatives of mycophenolic alcohols, aldehydes and acids with a C4-sidechain as defined in claim 4; pharmaceutical compositions containing them; uses thereof.

7. Claims: 4,11,18,25,32,39,46,50-55,60-63,68 partially

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Derivatives of mycophenolic alcohols, aldehydes and acids with a C6-sidechain as defined in claim 4; pharmaceutical compositions containing them; uses thereof.

8. Claims: 5,12,19,26,33,40,47,50-55,60-63,68 partially

Mycophenolic phosphates, phosphonates and sulfonates with a C2-sidechain as defined in claim 5; pharmaceutical compositions containing them; uses thereof.

9. Claims: 5,12,19,26,33,40,47,50-55,60-63,68 partially

Mycophenolic phosphates, phosphonates and sulfonates with a C2-sidechain as defined in claim 5; pharmaceutical compositions containing them; uses thereof.

10. Claims: 6,13,20,27,34,41,48 completely; claims 50-55, 60-63,68 partially

Mycophenolic hydrocarbyl derivatives as defined in claim 6; pharmaceutical compositions containing them; uses thereof.

11. Claims: 7,14,21,28,35,42,49-55,60-63,68 partially

Derivatives of mycophenolic diphosphates with a C2-sidechain as defined in claim 7; pharmaceutical compositions containing them; uses thereof.

12. Claims: 7,14,21,28,35,42,49-55,60-63,68 partially

Derivatives of mycophenolic diphosphates with a C4-sidechain as defined in claim 7; pharmaceutical compositions containing them; uses thereof.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/49231

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